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Aqueous suspension of oxendolone

Abstract:

The present invention relates to a stabilized aqueous suspension of oxendolone, which contains 0.05 to 1.0 w/v percent of a nonionic surfactant and 0.01 to 0.25 w/v percent of a p-hydroxybenzoic acid ester. The suspension satisfy the requirements of a pharmaceutical preparation and shows a prolonged activities of oxendolone without accompanying pain when it is injected.

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(54) Aqueous suspension of oxendolone.

(57) The present invention relates to a stabilized aqueous suspension of oxendolone, which contains 0.05 to 1.0 w/v percent of a nonionic surfactant and 0.01 to 0.25 w/v percent of a *p*-hydroxybenzoic acid ester.

The suspension satisfies the requirements of a pharmaceutical preparation and shows a prolonged activites of oxendolone without accompanying pain when it is injected.

EP 0 072 662 A2

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Aqueous suspension of oxendolone

This invention relates to a stabilized aqueous suspension of oxendolone.

Oxendolone is a generic name for 16β-ethyl-17β-hydroxy-4-estren-3-one, and it is known that the compound as well as various esters thereof have potent antiandrogenic activity (USP 3856829).

With a meagre solubility of 0.001% or less in water (25°C), oxendolone is so sparingly soluble and so much hydrophobic that if dispersed in water, its particles remain afloat, failing to give a suspension meeting the requirements of a pharmaceutical preparation. Incidentally, an aqueous suspension as a pharmaceutical product must satisfy various requirements such as a uniform dispersion of active component particles, a proper sedimentation rate on standing, a good redispersibility of particles and a satisfactory passage through the needle bore (for injectable preparations).

To impart such qualities to a pharmaceutical product, it is generally practiced to incorporate a thickening agent such as sodium carboxymethylcellulose,methylcellulose or the like, or, to increase the hydrophilicity of the product, a surfactant. Such procedures, if applied to the emulsification of oxendolone, would not lead to satisfactory results.

Under these circumstances the present inventors conducted an intensive study and found unexpectedly that, when

a nonionic surfactant and a p-hydroxybenzoic acid ester are added in suitable amounts to oxendolone or an ester thereof, the suspension characteristics of the compound are remarkably improved. This invention has been conceived and developed on the basis of the above finding.

This invention relates, therefore, to a stabilized aqueous suspension of oxendolone or an ester thereof characterized by containing 0.05 to 1.0 w/v % of a nonionic surfactant and 0.01 to 0.25 w/v % of a p-hydroxybenzoic acid ester.

Referring to oxendolone or said ester thereof which is employed in the aqueous suspension of this invention, the ester may, for example, be the acetate, propionate, valerate, caprylate, caproate, or the like. The number of carbon atoms in the ester is preferably small.

The non-ionic surfactant mentioned above includes, for example, sorbitan fatty acid esters such as polyoxyethylene sorbitan monolaurate (Tween 20, Polysorbate 20), polyoxyethylene sorbitan monopolmitate (Tween 40, Polysorbate 40), polyoxyethylene sorbitan monostearate (Tween 60, Polysorbate 60), polyoxyethylene sorbitan monooleate (Tween 80, Polysorbate 80), etc., hydrogenated castor oil polyoxyethylene glycol esters such as hydrogenated castor oil polyoxyethylene 40 Mol (HCO-40), 50 Mol (HCO-50), 60 Mol (HCO-60) and 80 MOL (HCO-80), etc., polyoxyethylene polyoxypropylene ethers such as Pluronic F 68 and Pluronic L 64 (Wyandot Co., U.S.A.), various other polyethylene glycol alkyl ethers, fatty acid monoglycerides, etc. Particularly preferred are Tween 20, Tween 80, HCO-50 and HCO-60. In terms of HLB number, it is generally desirable to use surfactants whose HLB numbers are within the range of from 8 to 18.

The p-hydroxybenzoic acid ester is exemplified by methyl, ethyl, propyl, butyl and other esters. These p-hydroxybenzoic acid esters may be used either alone or as a mixture of two or more species in combination with

said surfactant.

The proportion of said surfactant employed in the present invention generally falls within the ranges from 0.05 to 1.0 w/v % and preferably from 0.1 to 0.5 w/v %, though it may vary with the concentration of oxendolone and the amount of p-hydroxybenzoic acid ester. At concentrations below 0.05 w/v %, no uniform dispersion can be accomplished. If the amount of the surfactant is larger than 1.0 w/v %, it tends to encourage free settling and cause caking and other difficulties.

The proportion of p-hydroxybenzoic acid ester may also vary with the concentration of oxendolone, the amount of said surfactant added and the solubility of the p-hydroxybenzoic acid ester, and it ranges generally from 0.01 to 0.25 w/v %, and preferably from 0.1 to 0.2 w/v %. If its proportion is less than 0.01 w/v %, there occurs a free dispersion system giving rise to hard cakes.

Oxendolone or its ester is generally used in the concentration of 5 to 20 w/v %, and preferably in the range of 8 to 13 w/v %.

According to this invention, the aqueous suspension can be prepared by blending oxendolone or its ester, a non-ionic surfactant and a p-hydroxybenzoic acid ester in an optional order in accordance with per se known processes. A preferred production procedure is as follows.

Production Example

Ten (10) grams of microcrystalline particles of oxendolone are dispersed in 25 ml of a 0.8% solution of Tween 80.

Separately, an aqueous solution is prepared which contains 0.28% of ethyl p-hydroxybenzoate, 0.028% of propyl p-hydroxybenzoate, 1% of sodium carboxymethylcellulose, 16% of D-sorbitol and 2% of benzyl alcohol. This solution (50 ml) is added to the above oxendolone-Tween 80 solution and the mixture is made up to 100 ml with water and stirred well.

In the aqueous suspension according to this invention, it is of course possible to incorporate those auxiliary agents and additives which are commonly used in aqueous suspensions, e.g. thickening agents such as sodium carboxymethylcellulose, methylcellulose, etc. and isotonicating agents such as glucose, xylitol, inositol, sorbitol, mannitol, etc. It is also possible to incorporate local anesthetics such as benzyl alcohol, mepivacaine hydrochloride, procaine hydrochloride, etc. and preservatives such as chlorobutanol, phenol, etc.

The resulting aqueous suspension of this invention satisfies requirements for pharmaceutical use and, moreover, shows a prolonged activity of oxendolone without accompanying pain when it is injected.

Exmaple 1

Oxendolone	10 w/v %
Sodium carboxymethylcellulose	0.5
D-sorbitol	8
Benzyl alcohol	1

An aqueous suspension containing the above components is labelled Composition A. To aliquots of Composition A are added various stabilizers as indicated in Table 1 to prepare a series of preparations. These preparations were examined immediately after preparation and after 2 years of storage at room temperature for dispersion uniformity, sedimentation volume, redispersibility and ease of passage through the injection needle bore. The results are set forth in Table 1. It is apparent that the addition of stabilizers according to this invention produces remarkable effects.

Table 1

Formula	Storage / Evaluation parameters		Immediately after preparation: Dispersion uniformity	Immediately after preparation: Passage through needle bore	After 2 years of storage at room temperature: Sedimentation volume	After 2 years of storage at room temperature: Redispersibility	After 2 years of storage at room temperature: Passage through needle bore
Composition A			X	X	X	X	X
Composition A + Nonionic surfactant	Tween 20	0.2%	X	Δ	X	X	X
	HCO-40	0.3%	X	Δ	X	X	X
Composition A + p-Hydroxybenzoic acid ester*	M.P.	0.15%	X	X	X	X	X
	B.P.	0.02%	X	X	X	X	X
Composition A + Nonionic surfactant + p-Hydroxybenzoic acid ester*	Tween 20	0.2% +M.P. 0.15%	O	O	O	O	O
	HCO-60	0.2% +B.P. 0.02%	O	O	O	O	O
	Pluronic F 68	0.2% +B.P. 0.015%	O	O	O	O	O
	Tween 80	0.2% +M.P. 0.15% +B.P. 0.015%	O	O	O	O	O
	HCO-50	0.3% +E.P. 0.02% +M.P. 0.15%	O	O	O	O	O

Note) Dispersion uniformity:

O : The active component particles are evenly dispersed

X : The active component particles are afloat or have settled

Passage through the injection needle bore:

With a needle with a bore diameter of 150 μ

O : Aspirated easily

Δ : Aspirated with a slight resistance

X : Aspirated with a severe resistance

Redispersibility:

When shaken gently with a hand, it is evenly dispersed.

O : Shaken twice or less

X : Shaken ten or more times

Sedimentation volume:

O : The layer of suspended particles ≥30%

X : The layer of suspended particles <30%

*p-Hydroxybenzoic acid ester:

M.P.: Methyl p-hydroxybenzoate

E.P.: Ethyl p-hydroxybenzoate

P.P.: Propyl p-hydroxybenzoate

B.P.: Butyl p-hydroxybenzoate

Example 2

Oxendolone acetate	15 w/v %
Sodium carboxymethylcellulose	0.7
D-sorbitol	8
Benzyl alcohol	1
Tween 20	0.2
Methyl p-hydroxybenzoate	0.15
Propyl p-hydroxybenzoate	0.15

What we claim is:

1. A stabilized aqueous suspension of oxendolone or an ester thereof, which contains 0.05 to 1.0 w/v percent of a nonionic surfactant and 0.01 to 0.25 w/v percent of a p-hydroxybenzoic acid ester.

2. A suspension as claimed in Claim 1, wherein the nonionic surfactant is selected from the group consisting of polyoxyethylene sorbitan fatty acid esters, hydrogenated caster oil polyoxyethylene glycol esters and polyoxyethylene polyoxypropylene ethers.

3. A suspension as claimed in Claim 1, wherein the HLB number of the nonionic surfactant is within the range of from 8 to 18.

4. A suspension as claimed in Claim 1, wherein the p-hydroxybenzoic acid ester is a mixture of methyl p-hydroxybenzoate and propyl p-hydroxybenzoate.

5. A method for preparing a stabilized aqueous suspension of oxendolone or an ester thereof, which comprises adding 0.05 to 1.0 w/v percent of a nonionic surfactant and 0.01 to 0.25 w/v percent of a p-hydroxybenzoic acid ester.